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The effects of lower uterine segment involvement on angiolymphatic invasion, tumor grade, and staging ın patients with early-stage endometroid type endometrial cancer

Predictivity of lower uterine segment tumor

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Abstract

Aim: Endometrial cancer (EC) is the most common malignancy of the female reproductive system in developed countries. EC is surgically staged. EC's most important prognostic factors are stage, grade, lymphovascular space involvement (LVSI), and histologic subtype. We designed this study to determine the predictive value of lower uterine segment involvement (LUSI) in terms of angiolymphatic invasion, tumor grade, and lymph node involvement in patients with early-stage endometrioid type endometrial cancer (EEC).

Material and Methods: The study was performed as a retrospective clinical study in patients with stages 1A and 1B (FIGO 1988) who were operated for EEC (total abdominal hysterectomy + bilateral salpingo-oophorectomy (TAH+BSO) ± lymph node dissection) in the Gynecologic Oncology Clinic of Gazi University Hospital.

Results: Of the 98 patients in the study group, 53 (54.1%) had LUSI, while in the remaining 45 cases (45.9%), LUSI was negative. A statistically significant difference was found between LUSI and pelvic lymph node metastasis (p=0.049). There was a statistically significant difference between LUSI and depth of myometrial invasion (MI) (p=0.03). There was also a statistically significant difference between tumor diameter size and LUSI (p=0.001). However, LUSI was not substantial for other prognostic factors such as LVSI, tumor grade, and age.

Discussion: We showed that lower uterine segment involvement is important for myometrial invasion and pelvic lymph node metastasis and may determine the extent of surgery.

Keywords

Endometrioid-Type Endometrial Cancer, Lower Uterine Segment, Angiolymphatic Invasion, Myometrial Invasion, Endometrial Cancer Staging

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Introduction

Endometrial cancer is the most common malignancy of the female reproductive system in developed countries. It is the fourth most common cancer in women after breast, lung, and colorectal cancer [1]. The lifetime risk of developing EC is 2.6%, and the average age of onset is 62 years [2].

Approximately 80% of endometrial cancers diagnosed in developed countries are endometrioid type [3]. Prognosis, recurrence, and survival mainly depend on the surgical stage of the tumor. There are many risk factors for the development of EC, the majority being unmet estrogen and its causes. These include endometrial hyperplasia, polycystic ovary syndrome, obesity, nulliparity, infertility, history of infertility treatment, early menarche-late menopause, and prolonged estrogen exposure such as the use of estrogen therapy without progesterone at menopause. Medical conditions such as diabetes, hypertension, and hypothyroidism have also been shown to be associated with endometrial cancer. Conditions that decrease estrogen exposure or increase progesterone levels (such as oral contraceptives or smoking) have a protective effect [4].

The main complaint in 90% of endometrial cancer patients is abnormal vaginal bleeding, most commonly postmenopausal bleeding. Intermenstrual bleeding or prolonged heavy bleeding in perimenopausal and anovulatory premenopausal patients should also be suspected.

Endocervical curettage and endometrial biopsy should be performed in all patients with suspected endometrial cancer. Planning for definitive treatment is done in case of a positive endometrial biopsy. Stage, grade, lymphovascular area involvement, and histologic subtype are the most important prognostic factors in endometrial cancer. 70-80% of patients with endometrial cancer are stage 1 at the time of diagnosis. Stage 3 and stage 4 cancer are less common. The 5-year survival in stage 1 endometrial cancer is over 90% [5]. The first approach in the treatment of endometrial cancer is surgery. The surgical approach is total abdominal hysterectomy and bilateral salpingo-oophorectomy in the early stage, bilateral pelvic paraaortic lymphadenectomy and omentectomy in selected cases, and debulking in the advanced stage [5]. The therapeutic usefulness of systematic pelvic and paraaortic lymphadenectomy is controversial [5].

Lymphatic drainage of the uterus occurs in the pelvic lymph nodes, inguinal region, and paraaortic lymph nodes via the infundibulopelvic ligament. The frequency of lymph node metastasis in endometrial cancer varies between 7.7-21%. Of this rate, 3.3-12% is pelvic lymph node metastasis only, 2.5-8.8% is both pelvic and paraaortic metastasis, and 0.7-2% is paraaortic metastasis only. As pelvic lymph node involvement increases, paraaortic lymph node involvement also increases [6, 7, 8].

Endometrial carcinoma originates from the uterine corpus and fundus, but lower uterine segment involvement (LUSI) is observed in 3-6% of cases [9].

Tumors originating from the lower uterine segment (LUS) are located between the uterine corpus and cervix and show histologic features of both. Therefore, they sometimes complicate the differential diagnosis of uterine corpus and cervical adenocarcinomas when the primary tumor needs to be identified for further investigation and prognosis [10]. Tumors arising from or involving the LUS also differ from tumors of the uterine corpus by their thin mucosal and myometrial layers and poor hormonal response to estrogen [11].

In some reports, LUS carcinoma does not have the characteristics of type I endometrial cancer. It tends to show characteristics of type II, thought to be due to the thin endometrial layer of the LUS and a weak endometrial response to estrogen [12]. Clinically, type I cases are characterized by irregular menstruation, unmet estrogen, nulliparity, infertility, and a high frequency of PCOS (polycystic ovary syndrome). In contrast, type II cases show weak estrogen and progesterone receptors and p53 mutation expression and have similar features to LUS carcinoma [13, 14-17].

The endometrial layer of LUS carcinoma is similar to the endometrium in cell distribution and histochemistry, but the volume of the endometrium tends to be smaller in LUS [18]. Because the endocervical mucosa histologically transitions gradually to the LUS endometrium, endocervical and endometrial epithelial features show combinations in LUS.

Because cases of endometrial cancer originating from the LUS are rare, few studies have compared the characteristics of LUS tumors with tumors originating from the uterine corpus. There are conflicting reports on the effect of LUS involvement as a prognostic factor in endometrial cancer.

In this study, we aimed to investigate the effects of uterine lower segment involvement on lymph node involvement, myometrial invasion, angiolymphatic invasion, and staging in patients with early-stage endometrioid-type endometrial cancer.

Material and Methods

In cases operated for early-stage endometrioid type endometrial cancer, the predictive value of uterine lower segment involvement on lymph node involvement, myometrial invasion, angiolymphatic invasion, and staging was evaluated. Patients with histologic types other than endometrioid type endometrial cancer (serous, clear cell, undifferentiated, etc.), patients with advanced endometrial cancer, and patients who would not provide reliable data due to incomplete information were not included in the study. All patients who participated in the study were patients who underwent endometrial sampling due to perimenopausal or postmenopausal bleeding preoperatively and were diagnosed with endometrioid type endometrial cancer by pathology. TAH+BSO, bilateral pelvic lymph node dissection and ± paraaortic lymph node dissection were performed. The degree of myometrial invasion, tumor diameter size, histological grade, and cervical metastasis were evaluated by a frozen section of the hysterectomy slice. While only pelvic lymph node dissection was performed in patients with good prognostic data, total pelvic and paraaortic lymph node dissection was performed in the poor prognostic group with grade 3 tumor, myometrial invasion depth >1/2, tumor diameter >2cm, isthmus-cervix invasion, extrauterine disease (abdominal metastasis) invasion. Dissection was performed up to the renal vein level in surgically suitable cases. All materials were analyzed in our hospital's pathology laboratory. FIGO surgical staging system was used for endometrial cancer staging. FIGO was used for grade

classification, and the World Health Organization Classification of Tumors system was used for histological classification. Age, date of operation, type of operation, histological type of tumor, grade of tumor, diameter of tumor, percentage of tumor invasion into myometrium, stage of disease, number/location of lymph nodes removed, number/location of metastatic lymph nodes removed, presence of lymphovascular invasion, LUSI and surgical stage were evaluated.

In patients with LUSI, the depth of uterine myometrial invasion and tumor diameter, grade, and LVSI were evaluated to determine whether they were predictive values for lymph node involvement.

Statistical analysis

The research data were evaluated using the SPSS 17.0 statistical package program. Descriptive statistics were presented as mean, median (min; max), frequency distribution, and percentage. Pearson Chi-Square, Yates Corrected Chi-Square Test, and Fisher's Test were used as statistical methods. The statistical significance value was accepted as $p<0.05$.

Ethical Approval

This study was approved by the Ethics Committee of Gazi University Hospital (Date: 2017-04-24, No: 185).

Results

A total of 98 patients were included in the study. Patients underwent TAH+BSO, bilateral pelvic lymph node dissection, ± paraaortic lymph node dissection. The mean age of the patients in the study group was 61.2 (±9.3) years. The final pathology of all patients was endometroid-type adenocarcinoma. 12 (12.2%) patients were grade 1, 65 (66.3%) were grade 2, and 21 (21.4%) were grade 3.

After postoperative histopathologic evaluation, 17 (17.3%) patients were stage 1A, 65 (66.3%) were stage 1B, 7 (7.1%) were stage 3C1, and 8 (8.2%) were stage 3C2. The depth of myometrial invasion was below ½ in 42(42.9%) patients and above ½ in 56(57.1%) patients. Tumor diameter size was below 4 cm in 43(43.9%) patients and above 4 cm in 55(56.1%) patients. LVSI was positive in 25(25.5%) and negative in 72(73.5%) patients.

Of the 98 patients in the study group, 53(54.1%) had LUS involvement, and 45(45.9%) had no LUSI.

Of the 98 patients in the study group, 7 patients underwent only hysterectomy and salpingo-oophorectomy operation due to co-morbid diseases. The mean age of the patients with LUSI was 60.5(±9.19), while the mean age of the patients without LUSI was 62.0(±9.45).

Pelvic lymph node dissection was performed in 20 of 52 patients with LUSI, while pelvic paraaortic lymph node dissection was performed in 32 patients. Of 39 stage 1B patients without LUSI, 12 patients underwent hysterectomy + pelvic lymph node dissection, while 27 patients underwent pelvic + paraaortic lymph node dissection. Lymph node metastasis was detected in 11 patients with LUSI, while pelvic and paraaortic lymph node involvement was detected in 4 patients without LUSI (Table I).

No patients without myometrial involvement were among the 98 patients who participated in the study. A statistically significant difference was found between LUSI and MI depth (p=0.03). A statistically significant difference was also between LUSI and tumor diameter size (p=0.001). A statistically significant difference was found between LUSI and pelvic lymph node metastasis (p=0.049).

There was no statistically significant difference between LUSI, tumor grade, and LVSI (p=0.392 and p=0.852, respectively).

Table 1. Comparison of uterine corpus endometrioid tumors with and without LUSI

Variables		Group A N:53 LUSI (+)	Group B N:45 LUSI(-)	P
Age				
<60		28 (%52.3)	21 (%46.7)	0.543
≥60		25 (%47.2)	24 (%53.3)	
Tumor diameter				
(mean ±sd)				
<4 cm		15 (%28.3)	28 (%62.2)	0.001
≥4 cm		38 (%71.7)	17 (%37.8)	
Grade	1	8 (%15.1)	4 (%8.9)	0.392
	2	36 (%67.9)	29 (%64.4)	
	3	9 (%17)	12 (%26.7)	
MI				
<%50		28 (%52.8)	14 (%31.1)	0.030
≥%50		25 (%47.2)	31 (%68.9)	
LVSI (N, %)				
Positive		39 (%75)	33 (%73.3)	0.852
Negative		13 (%25)	12 (%26.7)	
Pelvic lymph node Metastasis (N)		10	2	0.049
Paraaortic lymph node Metastasis (N)		6	2	0.285
Ex		42 (%53.8)	36 (%46.2)	0.926
Alive		11 (%55)	9 (%45)	

Fisher's Exact test, Ki-re trend analysis, LUSI: Lower uterine segment involvement, MI: Myometrial invasion, LVSI: Lymphovascular space invasion, N: Number, P: Probability value

Discussion

Endometrial cancer is the most common gynecologic cancer in women in developed countries. Currently, most patients with endometrial cancer require surgical staging according to the FIGO staging system. Lymphadenectomy is one of the most controversial issues in endometrial cancer surgery[19]. Since lymph node metastasis in endometrial cancer affects the prognosis of the patient, lymphadenectomy has diagnostic value and therapeutic value.

LUS is anatomically located between the uterine corpus and cervix and shows histologic features of both of these parts. The main aim of our study is to perform lymph node surgery in patients with tumors located in the LUS only when necessary.

In our study, the mean age of the patient group with LUSI was 60.5(±9.19), while the mean age of the patient group without LUSI was 62.08(±9.45). Our study found no significant correlation between age and LUSI (p=0.543).

Brown et al. investigated whether LUSI was associated with the depth of MI and showed that LUSI was a determinant for the depth of myometrial invasion (p=0.02)[20]. In our study, LUSI was found to be associated with the depth of myometrial invasion (p=0.030). A study by Phelan et al. investigating whether LUSI was associated with tumor grade showed that LUSI was not a determinant of tumor grade (p=0.20)[21]. Of the 98 patients included in our study, the grade was 1 in 8(15.1%), 2 in 36(67.9%), and 3 in 9(17%) patients (p=0.392). Our study

found no significant correlation between tumor grade and LUSI. In a study by Gemer et al., age, depth of myometrial invasion, tumor grade, depth of myometrial invasion, depth of myometrial invasion lymphovascular area invasion were examined in patients with endometrial cancer with AUS involvement and evaluated whether they had predictive value for LUSI. In a retrospective study of 138 patients, tumor grade ($p = 0.002$), LVAI ($p = 0.01$), and depth of MI ($p < 0.001$) were statistically significant in patients with LUSI [22].

In a study by Erkaya et al., depth of MI, tumor grade, tumor diameter, lymph node metastasis, depth of myometrial invasion, and lymphovascular area invasion were examined in patients with endometrial cancer who had LUSI and evaluated whether they had predictive value for LUSI. In a retrospective study of 139 patients, tumor grade ($p<0.0001$), LVAI ($p<0.001$), depth of MI ($p<0.001$), and tumor diameter ($p=0.01$) showed a significant correlation in terms of LUSI. They also found that the risk of pelvic and paraaortic lymph node involvement increased in patients with AUS involvement, and this relationship was statistically significant ($p=0.001$ and $p=0.005$, respectively) [23]. In our study, LUSI was found to be associated with MI depth, tumor size, and pelvic lymph node involvement, which is consistent with the literature. However, no significant results were found in terms of LVSI and tumor grade. This may be related to the heterogeneity in tumor grade of the 98 patients included in our study. In addition, the effect of LUSI on survival was investigated in this study by Erkaya et al., but no significant difference was found ($p>0.05$).

A study by Kizer et al. evaluated whether LUSI is a predictive value for tumor grade and LVSI in endometrial cancer patients. In a retrospective study of 481 patients, LVSI was found to be associated with LUSI. It was reported that LUSI was associated with decreased survival[24]. In our study, LUSI was not found to be statistically significant for LVSI. This may be due to the need for more cases in the study to evaluate the association with LUSI.

A study by Madom et al. evaluated whether LUSI, MI, and LVSI have a predictive value in terms of lymph nodes in endometrial cancer patients. In a retrospective study of 324 patients, LVSI, LUSI, and MI were found to be predictive of lymph node involvement [25].

Of the 97 patients included in our study, 25(25.7%) had LVSI, and 72(74.3%) did not have LVSI. Eight of 25(25.7%) patients with LVSI had lymph node metastasis, while 8 of 72(74.3%) patients without LVSI had lymph node metastasis, and this was statistically significant ($p=0.044$). Of the 15 patients with lymph node metastases, 7 had LVSI.

LVSI was added to the 2023 FIGO Endometrial cancer staging updated last year, and the disease is considered stage 2 when diffuse LVSI is present.

Conclusion and Limitation

Understanding the prognostic value of LUSI may be useful in planning the extent of surgery, adjuvant treatment, and survival. Prospective studies with more patients are needed for more meaningful results to have the last word on the subject.

The research(thesis study) was presented at the 1st International and 16th National Gynecologic Oncology Congress (November 21st - 25th, 2018) held in Antalya. (Oral Presentation-31).

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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